UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,988	12/31/2001	Avigdor Levanon	10793/46	7233

26646 7590 06/06/2006

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,988	LEVANON ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-57,61-67,72-80 and 98-141 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-57,61-67,72-80 and 98-141 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/13/06; 7/14/2005; 4/29/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: IDS. 6/7/04; 4/26/04; 1/27/03 8/6/02

DETAILED ACTION

Claims 1-7, 9, 30-34, 37, 39-43, 45, 49, 55, 62 and 98 have been amended Claims 58-60, 68-71 and 81-97 have been canceled. Claims 99-141 have been added. Claims 1-57, 61-67, 72-80 and 98-141 are pending and under consideration.

The instant invention is given the effective filing date of December 31, 2001, for the reasons set forth in the previous Office action under the heading of Priority".

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12, 14, 17-19, 23, 26-48, 99-102, 104, 107-109, 111-113, 116-123, 125, 128-130, 132-134, 137-141 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant antibody multimers read on natural antibodies found within humans, and is rejected under 101 as a product of nature. When given the broadest reasonable interpretation, the claimed dimers, trimers and tetramers read on a dimeric IgA, or a trimeric IgA molecule joined by their respective tailpieces to the J chain (Abbas et al, Cellular and Molecular Immunology, 1991, pp. 47, second column, lines 11-18 and page 49, legend for Figure 3-6). Claims requiring a tetramer read on an IgA dimer, having four heavy chains as an antigen-binding fragment and four light chains as an antigen-binding fragment. Claims requiring the linkage of the first and second antigen-binding fragments read on the cysteine linkages between a light chain and a heavy chain, and the cysteine linkages joining two heavy chains. such as the linkages found in a IgG molecule. The tailpiece segments of IgA and IgM incorporate a carboxyl terminal 18 amino acid sequence serving as a linker to the J chain, thus the 18-mer "tailpiece" fulfills the requirements of a linker comprising 5-20

amino acids. Amendment of the instant claims to specify "isolated" antibody multimer would overcome this rejection.

Claims 72 and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of pharmaceutical composition" in claim 72 lacks antecedent basis in claim 48.

Claims 1-34, 49-57, 61-67, 74-80 and 98-141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) Claims 1, 4 and 7 have been amended to require that the antibody multimers are multimers of human antibodies. The specification discloses that the human scFv antibodies Y1 and N14 were isolated from a human antibody phage display library (page 34, paragraph 150 and page 48, paragraph 195) and further states that "One example of an antibody of the present invention that binds to epitopes of formulae I-III" is the fully human antibody Y1 (page 41, paragraph 167). These statements do not provide support for the amendment of the instant claims to human antibodies because the description of two individual antibody clones, Y1 and N14, which were derived from a phage display library of human antibody sequences, do not adequately describe the claimed genus of antibody multimers which include any antibody which binds to the described sequence motif. One of skill in the art upon reading of the instant specification which describes two antibody clones extracted from a phage display library of human sequences would not conclude that the entire invention was restricted to only human antibodies which bound to the described sequence motif. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus of human antibody multimers at the time of filing.

(B) Claim 45 has been amended to alter the sequence to which the claimed antibody multimer binds. However, the amended sequence was not present in the originally filed disclosure.

The rejection of claims 35, 36, 38-44 and 46-48 under 35 U.S.C. 102(b) as being anticipated by Ward et al (Biochemistry, 1996, Vol. 35, pp. 4929-4938, reference of the IDS filed January 27, 2003) is maintained for reasons of record. Claims 37, 45, 72 and 73 are also rejected for the same reasons of record.

Claim 35 is drawn to an antibody multimer comprising a first and a second antigen-binding fragment, wherein said first or second antigen binding fragment is capable of cross reacting with two or more epitopes, each epitope comprising one or more sulfated tyrosine residues and at least one cluster of two or more acidic amino acids. Claim 36 embodies the multimer of claim 35 wherein said multimer is capable of cross reacting with PSGL-1. Claim 37 embodies the multimer of claim 35 that binds to QATEYEYLYDFLPETE wherein at least one tyrosine residue is sulfated. Claim 38 embodies the antibody multimer of claim 35 wherein the multimer is capable of cross-reacting with GP1b-alpha. Claim 39 embodies the multimer of claim 35 that binds to DEGDTDLYDYYPEEDTEGD, wherein at least one tyrosine residue is sulfated. Claim 40 embodies the multimer of claim 35 that binds to TDLYDYYPEEDTE, wherein at least one tyrosine residue is sulfated. Claim 41 embodies the multimer of claim 35 that binds to DEGDTDLYDYYP, wherein at least one tyrosine residue is sulfated. Claim 42 embodies the antibody multimer of claim 35 that binds to YDYYP, wherein at least one tyrosine residue is sulfated. Claim 43 embodies the multimer of claim 35 that binds to TDLYDYYP, wherein at least one tyrosine residue is sulfated. Claim 44, 46 and 47 embody the multimer of claim 35 wherein the multimer is capable of cross reacting with fibrinogen-gamma prime, heparin and complement compound 4, respectively. Claim 45 embodies the multimer of claim 44 that binds to EHPAETEYDSLYPED, wherein at least one tyrosine residue is sulfated. Claim 48 embodies the multimer of claim 35 that is capable of cross-reacting with at least one cell selected from the group consisting of B-CLL cells, AML cells, multiple myeloma cells and metastatic cells. Claim 72 is drawn to a pharmaceutical composition of claim 48 in an amount effective to inhibit metastasis. Claim 73 is drawn to a pharmaceutical composition comprising

the antibody multimer of claim 48 in an amount effective to inhibit growth and or replication of tumor cells, increase the mortality of tumor cells or increase the susceptibility of tumor cells to damage by anticancer agents.

Ward et al disclose antibody SZ2 which binds the epitope of Tyr-276 to Glu-282, YDYYPEE (4935, first column, lines 19-21) of GP1b-alpha, which fulfills the specific embodiment of claims 35, 39, 40 and 42 as the YDYYPEE epitope is comprised within the sequences of claims 39 and 40. The SZ2 antibody also fulfills the specific embodiments of claims 1, 2, 4 and 5 because the epitope the peptide comprises the sequence YDYYPEE which was disclosed by Ward et al to be 90% sulfated on Tyr 278 and 279 and 50% sulfated on Tyr 282. Ward et al disclose the peptide of DEGDTDLYDYYPEEDTEGD (page 4930, first column, line 44) which fulfills the specific embodiments of claims 4 and 5 with (Y)r=0, because z=1, (W)z=Gly, P(first)=Asp-Thr-Asp as (A)n(X)u(A), P(second)=Leu as (A)n, wherein m and u=0, sulfo-Try, P(third) as (A)n=Asp, wherein m and u=0, t=2 and (Y)t=sulfo-Try-sulfo-Tyr, P(forth)=Pro-Glu-Glu-Asp as (X)u(A)n(A)m, wherein u and m=1 and n=2 and (X)u=Pro, (A)n=Glu and (A)m is Asp. Said epitope also fulfills the specific embodiment of claims 1 and 2 wherein z=0, P(first)=(A)n(X)u(A)m, wherein, n=u=m=1 and wherein (A)n=Asp, (X)u=Thr and (A)m=Asp; t=1 and (Y)t=sulfo-Try; and wherein P(second)=(A)m(A)n(X)u, wherein n and u are 0 and wherein (A)m is Asp. The claims also fulfill the specific embodiments of claim 2 because W is Gly, Y is sulfo-Tyrosine, one "A" is Asp, and q is 1.

It would be inherent in the binding affinity of the SZ2 antibody that it would cross-react with epitopes comprising DEGDTDLYDYYP, TDLYDYYP and EHPAETEYDSLYPED,, wherein at least one tyrosine residue is sulfated; it would also be inherent in the binding affinity of the SZ2 antibody that it would bind to at least one cell selected from the group consisting of B-CLL cells, AML cells, multiple myeloma cells and metastatic cells and that it would cross react with fibrinogen-gamma prime, heparin and complement compound 4, because the structure of the antibody determines its binding specificity and cross-reactivity.

Ward et al also anticipates multimers which are dimers or trimers, because when given the broadest reasonable interpretation the SZ2 antibody is a dimer in that it has two identical heavy chain and light chain proteins as the first and the second antigen binding fragments which are linked by a natural disulfide bridge inherent in the structure of the antibody, thus anticipating

claims 9, 10, 12 and 26. The SZ2 antibody is also a trimer comprising three CDR regions, which are antigen-binding regions, on either the heavy chain or light chain, wherein said CDR regions are linked by polypeptides which fulfill the specific embodiments of a polypeptide linker of claims 17 and 19.

Applicants arguments regarding the lack of a disclosure of a human antibody by Ward et al are moot in light of the fact that claim 35 does not require a human antibody sequence.

The rejection of claims 35, 36, 38-44, 46-48 under 35 U.S.C. 102(b) as being anticipated by Snapp et al (Blood, 1998, Vol. 91, pp. 154-164, reference of the IDS filed January 27, 2003) is maintained for reasons of record. Claims 37, 45 , 72 and 73 are also rejected for the same reasons of record..

Snapp et al disclose the monoclonal antibody KPL1 which binds to amino acids residues 5-11 (YEYLDYD) of PSGL-1, wherein at least one tyrosine is sulfated (page 161, second column, lines 7-10, page 162, second column, lines 39-41 and page 157, first column, lines 10-12), thus fulfilling the specific embodiments of claims 35-37 because the YEYLDYD epitope is comprised within the sequences of claims 36 and 37. The peptide of YEYLDYD fulfills the specific embodiments of claim 1 with z=0, m and u=0 and P(first) is (A)n=Glu and P(second)=(A)n(A)m(X)u, wherein n=1, m=1 and u=0 and therefore (A)n=Leu and (A)m=Asp. Snapp et al also disclose that the KPL1 antibody binds to human myeloma cells (page 160, second column, lines 8-10), thus fulfilling the specific embodiment of claim 48, specifying multiple myeloma cells.

It would be inherent in the binding affinity of the KPL1 antibody that it would cross-react with epitopes comprising DEGDTDLYDYYPEEDTEGD, YDYYPEE and EHPAETEYDSLYPED, wherein at least one tyrosine residue is sulfated; it would also be inherent in the binding affinity of the KPL1 antibody that it would cross react with fibrinogen-gamma prime, heparin and complement compound 4, because the structure of the antibody determines its binding specificity and cross-reactivity.

Snapp et al also anticipates multimers which are dimers or trimers, because when given the broadest reasonable interpretation the KPL1 antibody is a dimer in that it has two identical heavy chain and light chain proteins as the first and the second antigen binding fragments which

are linked by a natural disulfide bridge inherent in the structure of the antibody, thus anticipating claims which require a dimer.

Applicant argues that the publication of Thatte et al (2002) teaches that the antibody of Snapp, KPL1, does not require sulfation for binding to its target. this has been considered but not found persuasive. Firstly the MPEP states

Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976).

Therefore, the Snapp reference retains its validity when applied against the instant pending claims. Secondly, a statement that the antibody does not require the sulfation of the epitope for binding does not exclude the antibody from binding to the epitope when sulfated. There is o statement in Thatte et al which teaches that the antibody does not bind to the epitope when sulfated. Thirdly, the specification identifies PSGL-1 as a human protein known to be tyrosine sulfated on page 40, paragraph 166, thus admitting that antibodies which bind to the sulfated epitope of PSGL-1 are prior art.

The provisional rejection of claims 1-28 and 32-48 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-21 and 23-117 of copending Application No. 10/032,423 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant antibody multimers comprise the individual antibodies of the co-pending application. Thus the instant antibody multimers are obvious variants over the antibodies of the '423 application.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of Applicant's amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
5/23/2006